REMARKS

I. Status of the Claims

Claims 1-16 were canceled in a Preliminary Amendment submitted September 04, 2003. Claims 17-25 were canceled in an Amendment and Response to Restriction Requirement submitted October 14, 2003. Claims 34-36 were amended and new claim 40 was added in an Amendment submitted February 18, 2004. Claims 26 and 30 have been amended and new claim 41 has been added in the Amendment submitted herewith. Claims 26-41 are therefore pending in the application. Support for newly added claim 41 can be found in claim 5 as originally filed.

II. Claims Rejected Under 35 U.S.C. § 112, Second Paragraph

Claims 26-40 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is asserted in the Action, that it is unclear if the recitation of "HIV-gp160 sequence" is directed to an amino acid or nucleic acid sequence. It is further alleged that it is unclear what is intended by the recitation of "part" of all the gp160 sequence. Applicant respectfully traverses this rejection.

At the time the present application was filed, it was known in the art that the *env* gene of HIV-1 encodes a glycoprotein referred to as gp160, and that the term gp160 refers to the full length gp160 polypeptide. The gp160 protein is cleaved intracellularly to yield gp120 and gp41 fragments. Applicant's use of the term "part or all of" the gp160 sequence, in the claims and specification, refers to the gp120 cleavage product (*i.e.*, "part" of the gp160 sequence) and the full length gp160 (*i.e.*, "all" of the gp160 sequence), respectively. However, to expedite the allowance of claims in the present application, Applicants have amended claims 26 and 30, to recite "a nucleic acid sequence encoding the HIV-1 gp160 or

gp120 polypeptide sequence". Applicants assert that the claims as amended distinctly claim the subject matter which applicant regards as the invention, and as such, respectfully request withdrawal of the rejection of claims 26-40 under 35 U.S.C. § 112, second paragraph.

Claims 26-40 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Action alleges that the recitation of "immune response against HIV-1 infection" is deemed indefinite, as it is unclear how an "immune response can be directed to an infection". Applicant respectfully traverses this rejection.

It is known in the art of immunology, that an "infection" occurs when a particular pathogen (*e.g.*, a virus) is capable of evading or circumventing the host organism's immune defenses (*e.g.*, a humoral and/or cell-mediated immune response). It is also known that a host organism (*e.g.*, a human) can be immunized against "infection" by a particular pathogen via administering one or more antigenic components of the pathogen to the host organism (or by administering a vector which expresses genes encoding said antigenic components), thereby priming the host organism's immune defenses to mount an "immune response" against the pathogen "infection".

The present invention has identified such antigenic components of HIV-1 (*i.e.*, the gp160 polypeptide and gag polypeptide) necessary for "producing an immune response against HIV-1 infection", wherein the antigenic component gp160 is expressed by a recombinant adenovirus vector, as set forth in independent claim 26. Applicants therefore assert that the phrase "immune response against HIV-1 infection" is definite and distinctly claims the subject matter which applicant regards as the invention, and as such, respectfully request withdrawal of the rejection of claims 26-40 under 35 U.S.C. § 112, second paragraph.

III. Claims Rejected Under 35 U.S.C. § 112, First Paragraph

Claims 29-40 are rejected under the 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Action asserts that the "teaching of the specification is not enabling", as the "breadth of the invention encompasses HIV vaccine for an anti-HIV treatment". The Action alleges that Applicant has not provided any convincing evidence that their immunogenic composition is indeed useful for an anti-HIV treatment in HUMAN and have not provided sufficient guidance to allow one skilled in the art to practice the claimed invention with a reasonable expectation of success and without undue experimentation. Applicant respectfully traverses this rejection.

The claims pending in the present application are directed to a method for producing an immune response against HIV-1 infection in a human comprising administering to the human an immunogenic composition comprising a recombinant adenovirus, wherein the adenovirus comprises an expression cassette containing a promoter, a nucleic acid sequence encoding the HIV-1 gp160 or gp120 polypeptide sequence and a polyadenylation signal sequence.

The enablement requirement of 35 U.S.C. § 112, first paragraph, requires that the specification describe how to make and use the invention as it is defined by the claims, such that a person of skill in the art can practice the invention without undue experimentation. As set forth above, the claims are directed to a method of producing an immune response against HIV-1 infection. Applicant's specification (1) clearly demonstrates that the claimed methods of the instant invention produce strong neutralizing antibodies (*i.e.*, an immune response) in dogs and chimpanzees, and further protected the chimpanzees (*i.e.*, an immune response) from challenge with HIV-1 (*e.g., see* page 30, line 21 through page 38, line 10). The specification also discloses how to make and use recombinant adenovirus expression cassettes encoding gp160 (or gp120), the gag and/or env polypeptide subunits and the prime/boost immunization regimens. Thus, Applicants assert that the specification describes

how to make and use the claimed invention in such as way as to enable one of skill in the art to practice the invention without undue experimentation.

The Action alleges however, that there are numerous scientific obstacles related to HIV infection and treatment which "establish that the contemporary knowledge in the art would not allow one of skilled in the art to use the claim invention with a reasonable expectation of success and without undue experimentation". Applicant disagrees with this allegation. "The test of enablement is not whether any experimentation is necessary, but whether if experimentation is necessary, is it undue" (*In re Angstadt*, 537 F.2d 498; 190 U.S.P.Q. 214). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. Applicant asserts that the specification enables one of skill in the art to make and use the claimed invention without undue experimentation and that the *in vivo* data clearly indicates that the claimed invention can be practiced with a reasonable expectation of success.

The Action further states that non-human animals, particularly chimpanzees, are not convincing models of HIV-1 infection in humans and that human clinical trials using immunological based therapies have not yielded successful results in the treatment and/or prevention of HIV infection. Applicant contends that chimpanzees, at the time the present application was filed, were the best (non-human) *in vivo* model for studying HIV-1 infection and for testing HIV immunogenic compositions. Finally, Applicant submits herewith a series of tables obtained from the HIV Vaccine Trials Network (**Exhibit A**) which list ongoing phase I and II clinical trials, wherein the same antigenic components claimed in the present application (*i.e.*, env and gag) are undergoing testing as polypeptide subunit and/or vector based immunogenic compositions.

In particular, protocol numbers HVTN 050 (gag) and HVTN 054 (gag-pol and env) describe human clinical trials utilizing adenovirus vectors which are already enrolling human patients or will do so shortly. Although the Patent and Trademark Office does not serve to

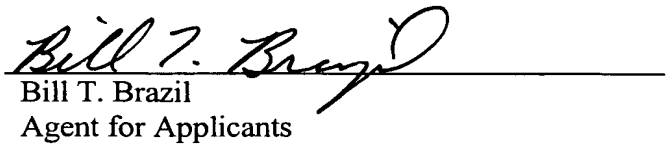
function as a second Food and Drug Administration, and human clinical trial results are not necessary to establish patentability, the fact that the FDA is permitting human clinical trials to proceed using adenovirus vectors expressing the HIV env and gag genes, serves to satisfy the Wands factors cited by the Examiner.

Thus, Applicants assert that the specification enables one of skill in the art to make and use the claimed invention without undue experimentation and with a reasonable expectation of success, and as such, respectfully request withdrawal of the rejection of claims 26-40 under 35 U.S.C. § 112, first paragraph.

If there are any matters which may be resolved or clarified through a telephone interview, the Examiner is requested to contact the undersigned Agent at the number indicated.

The notice set a three-month period to comply, to and including June 19, 2004. Thus, this response is believed to be timely filed. Should any fees be deemed necessary, the Commissioner is authorized to deduct said fees from Deposit Account No. 01-1425.

Respectfully submitted,



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Ongoing HVTN Trials, (slide 1 of 2)

Protocol Number	Status as of April 2004	Prime				Boost				Ref
		Class	Producer	Product Name	Adjuvant	Class	Producer	Product Name	Adjuvant	
HIVNET 026 (n=160)	Immunizations completed	Canarypox vector (clade B Env, Gag, Pro, RT, Nef)	Aventis Pasteur	ALVAC vCP1452		Protein subunit (clade B Env)	VaxGen	gp120 MN	Aluminum hydroxide/ thimerosol	
HVTN 039 (n=110)	Immunizations completed	Canarypox vector (clade B Env, Gag, Pro, RT, Nef)	Aventis Pasteur	ALVAC vCP1452 (high-dose)						Goepfert P, et al. 10th CROI, Feb 10-14, 2003; Boston. Abs #82
HVTN 040 (n=48)	Enrolling in South Africa	VEE vector (clade C Gag)	AlphaVax	AVX-101						
HVTN 041 (n=84)	Immunizations completed	Protein (clade B Nef-Tat fusion protein + clade B Env subunit)	GlaxoSmith Kline	NefTat + gp120W61D	AS02A					
HVTN 042/ANRS VAC19 (n=174)	Enrolling	Canarypox vector (clade B Env, Gag, Pro, RT, Nef)	Aventis Pasteur	ALVAC vCP1452		Lipopeptides (poly-epitopic: clade B Gag, Pol, Nef)	Aventis Pasteur/ ANRS	LIPO-5		
HVTN 044 (n=60)	Enrolling	DNA plasmids (clade B Gag-Pol-Nef; clade A,B,C Env)	NIH VRC	VRC-HIVDNA-009	DNA plasmid cytokine (IL2-Ig)					
HVTN 045 (n=30)	Immunizations completed	DNA plasmid (clade B Env, Gag, Pro, RT, Tat, Vpu, Rev)	Emory Univ. (H. Robinson)	pGA2/JS2 DNA						

Ongoing HVTN Trials, (slide 2 of 2)

Protocol Number	Status as of April 2004	Prime				Boost				Ref
		Class	Producer	Product Name	Adjuvant	Class	Producer	Product Name	Adjuvant	
HVTN 048 (n=42)	Enrollment completed	DNA plasmid (poly-epitopic: Gag, Pol, Vpr, Nef, Rev, and Env)	Epimmune	EP HIV-1090						
HVTN 049 (n=168)	Enrolling	DNA plasmids (clade B Gag, Env)	Chiron	Gag and Env DNA/PLG microparticles	PLG	Protein subunit (clade B Env)	Chiron	Oligomeric, V2-deleted HIV gp140 SF-162		
HVTN 050/Merck 018 (n=435)	Enrolling in North America, South America, Southeast Asia	Non-replicating adenovirus vector (clade B Gag)	Merck	MRKAd5 HIV-1 Gag						
HVTN 052 (n=180)	Enrolling	DNA plasmids (clade B Gag-Pol-Nef; clade A,B,C Env)	NIH VRC	VRC-HIVDNA-009		*See HVTN 057*				

Planned HVTN Trials: Phase I (including Phase Ib and Phase I/II), April 2004 (slide 1 of 2)

Protocol Number	Anticipated Start Date	Prime				Boost			
		Class	Producer	Product Name	Adjuvant	Class	Producer	Product Name	Adjuvant
HVTN 055 (n=150)	Q2 2004	MVA vectors (clade B Env, Gag; Tat, Rev, Nef, Pol)	Therion	TBC-M358; TBC-M335		Fowlpox vectors (clade B Env, Gag; Tat, Rev, Nef, Pol)	Therion	TBC-F357;TBC-F349	
HVTN 056 (n=96)	Q2 2004	Peptides (polyepitopic: clade B Env, Gag, Nef)	Wyeth	Wyeth multiepitope CTL peptide vaccine	RC-529-SE, GM-CSF	*See HVTN 061*			
HVTN 061 (n=96 (HVTN 056 rollover))	Q4 2004	*See HVTN 056*				DNA plasmid (clade B Gag)	Wyeth	WLV003	DNA plasmid cytokine (IL-12) + bupiva-caine
HVTN 054 (n=48)	Q3 2004	Non-replicating adenovirus vectors (clade B Gag-Pol; clade A,B,C Env)	NIH VRC	VRC-ADV-014					
HVTN 058 (n=30)	Q3 2004	DNA Plasmid (clade B Gag, Pro, RT, Env, Tat, Rev, Vpu)	GeoVax	HIVB DNA pGA2/JS7#2					

Planned HVTN Trials: Phase I (including Phase Ib and Phase I/II), April 2004 (2 of 2)

Protocol Number	Anticipated Start Date	Prime				Boost			
		Class	Producer	Product Name	Adjuvant	Class	Producer	Product Name	Adjuvant
HVTN 059 (n=96)	Q3 2004	VEE vector (clade C Gag)	AlphaVax	AVX-101					
HVTN 057 (n=180 (HVTN 052 rollover))	Q4 2004	*See HVTN 052*				Non-replicating adenovirus vectors (clade B Gag-Pol-Nef; clade A,B,C Env)	NIH VRC	VRC-ADV-014	
HVTN 060 (n=144)	Q4 2004	DNA plasmid (clade B Gag)	Wyeth	WLV003	DNA plasmid cytokine (IL-12) + bupivacaine	*Wyeth peptides (see 056 prime)*			
TBD	Q4 2004		SAAVI	SAAVI-pThr.grttnC; SAAVI-pThr.gp150CT					
TBD	2005	DNA plasmid (polyepitopic: Gag, Pol, Vpr, Nef, Rev, Env)	Epimmune	EP HIV-1233		MVA Vector (poly-epitopic: Gag, Pol, Vpr, Nef, Rev, Env)	Bavarian-Nordic	MVA-mBN32	
TBD	2005	Protein (containing T-helper epitopes from clade B Env, Gag, Pol, Vpu) + DNA plasmid (polyepitopic: Gag, Pol, Vpr, Nef)	Epimmune	EP-1043 + EP HIV-1090	Alum (for EP-1043 only)				
TBD	2005	MVA Vector (clade B Gag, Pol, Env)	GeoVax	MVA-HIV 62					

Planned HVTN Trials: Phase II, April 2004

Protocol Number	Anticipated Start Date	Prime				Boost			
		Class	Producer	Product Name	Adjuvant	Class	Producer	Product Name	Adjuvant
HVTN 204 (n=700)	Q4 2004	DNA plasmids (clade B Gag-Pol-Nef; clade A,B,C Env)	NIH VRC	VRC-HIVDNA-009		Non-replicating adenovirus vectors (clade B Gag-Pol; clade A,B,C Env)	NIH VRC	VRC-ADV-014	

Completed HVTN Trials, April 2004

Protocol Number	Year Completed	Prime				Boost			
		Class	Producer	Product Name	Adjuvant	Class	Producer	Product Name	Adjuvant
HVTN 203 (n=330)	2003	Canarypox vector (clade B Env, Gag, Pro, RT, Nef)	Aventis Pasteur	ALVAC vCP1452		Protein subunit (clade B Env)	VaxGen	AIDSVAX B/B (gp120 MN, gp120 GNE8)	Aluminum hydroxide gel